EXHIBIT 602.9

Disposition of Toxic Drugs and Chemicals in Man

Seventh Edition

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BIOMEDICAL PUBLICATIONS
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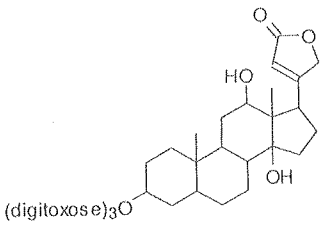
Digoxin



T½: 30–45 hr
Vd: 5.1–7.4 L/kg
Fb: 0.20

Occurrence and Usage. Digoxin (Lanoxin) is a cardiotonic plant glycoside that occurs in *Digitalis lanata* in combination with glucose and acetic acid. It is the 12-hydroxy analogue of digitoxin and is a major metabolite of that compound in man. In the treatment of congestive heart failure, digoxin is commonly given in daily oral maintenance doses of 0.25–0.75 mg; when initiating therapy, loading doses of 0.75–1.5 mg by intravenous or intramuscular injection or 2–3 mg orally may be administered. It is supplied in tablets of 0.125–0.5 mg, an elixir of 0.25 mg/5 mL and ampules containing 0.25 mg/mL.

Blood Concentrations. A single oral 0.25 mg digoxin dose administered to 6 fasting normal subjects resulted in serum concentrations that peaked at 1.13 μg/L at 1 hour and declined to 0.32 μg/L by 6 hours (Panisset et al., 1973). Peak plasma concentrations following a single 0.5 mg oral dose in 5 subjects averaged 1.4 μg/L at 2 hours on a full stomach and 2.4 μg/L at 1 hour when fasting (White et al., 1971). Serum concentrations after a single intravenous 0.75 mg dose are initially as high as 13 μg/L at 10 minutes after injection but decline rapidly (Koup et al., 1975). Serum digoxin concentrations in 131 controlled patients receiving an average daily oral dose of 0.31 mg (range, 0.0625–1.0) averaged 1.4 μg/L (range, 0.3–3.0) (Smith and Haber, 1970). Blood for serum digoxin analysis should be drawn at least 6 hours after the last dose to avoid erroneously high values (Murphy et al., 1985).

Digoxin, unlike digitoxin, exhibits negligible binding to plasma proteins (Doherty et al., 1971) and distributes nearly equally between erythrocytes and plasma (Abshagen et al., 1971). The average elimination half-life in normal subjects is 37 hours (Huffman et al., 1974). The bioavailability of oral preparations ranges from 67% for tablets to 100% for an encapsulated elixir (Aronson, 1980). Recent data strongly suggests that digoxin follows nonlinear kinetics (Wagner et al., 1981).

Serum digoxin concentrations are effectively doubled during the co-administration of quinidine or quinine; this may result from a reduction in the binding of digoxin to skeletal muscle (Chen and Friedman, 1980; Leahey et al., 1980; Wandell et al., 1980; Schenck-Gustafsson et al., 1981).

Metabolism and Excretion. The oral bioavailability of digoxin ranges from 67–97%, depending on the formulation. The drug is biotransformed to only a small degree in man. The metabolites are largely products of hydrolytic cleavage of the digitoxose group and of sulfate and glucuronide conjugation (Okita, 1964). An average of 59% of a single dose is excreted in the urine over a 7 day period, of which 95–98% is unchanged drug; an average of 15% is excreted in the feces over the same period (Marcus et al., 1964; Doherty et al., 1970). In a 5 day period, 2% of a dose is eliminated as digoxigenin-bis-digitoxoside, 0.8% as digoxigenin-mono-digitoxoside, 0.3% as digoxigenin and 0.3% as dihydrodigoxin (Gault et al., 1979). During chronic oral therapy, an average of 57% of a dose appears in the daily urine as apparently unchanged drug and urine concentrations are on the order of 25–125 μg/L (Huffman et al., 1974).

Myocardial/serum digoxin concentration ratios average 149 in infants and 28 in adults during therapy (Park et al., 1982). The following tissue distribution of the drug was determined from 17 adult patients who had been maintained on a mean daily dose of 0.005 mg/kg digoxin and who had not exhibited signs of toxicity prior to death (Andersson et al., 1975):

Digoxin Tissue Distribution During Therapy (μg/kg)*

	Brain	Atrial Myocardium	Ventricular Myocardium	Liver	Kidney	Skeletal Muscle	Fat
Average	32	65	133	72	128	30	10
(Range)	(3–74)	(27–129)	(50–296)	(29–186)	(56–253)	(13–56)	(4–23)

* By ^{86}Rb uptake inhibition after dichloromethane extraction

Toxicity. Digoxin toxicity is manifested by nausea, vomiting, diarrhea, blurred vision and cardiac disturbances such as tachycardia, premature contractions, atrial fibrillation and atrioventricular block. Psychosis with vivid hallucinations has been described (Carney et al., 1985). Serum concentrations averaged 3.7 μg/L (range, 1.6–13.7) in 48 patients exhibiting toxic signs who were being maintained on a mean dose of 0.36 mg (range, 0.125–1.0) daily (Smith and Haber, 1970). A series of clinical reports of nonfatal and fatal digoxin poisoning have described cases of oral overdosage with 2.5–25 mg of the drug in which serum concentrations of 11–42 μg/L and elimination half-lives of 5–48 hours were observed (Smith and Willerson, 1971; Hobson and Zettner, 1973; Watanabe et al., 1977; Pearce et al., 1980). One subject who self-administered 200 mg of digoxin intravenously developed a maximum serum concentration of 52 μg/L after 4 hours and died after 6 hours (Reza et al., 1974). Antidotal treatment of a case of ingestion of 22.5 mg was successfully accomplished by the intravenous administration of digoxin-specific antibodies (Smith et al., 1976). Several authors have obtained benefit with charcoal hemoperfusion (Smiley et al., 1978; Marbury et al., 1979), while others do not recommend its use (Warren and Fanestil, 1979; Rowett, 1980); orally-administered charcoal has been reported to markedly shorten the elimination half-life (Boldy et al., 1985), as has cholestyramine (Roberge and Sorensen, 2000). Atropine and phenytoin have been found to completely reverse digoxin-induced arrhythmias (Ekins and Watanabe, 1978). Severe poisoning may require the administration of digoxin-specific antibody fragments (Antman et al., 1990).

Reported postmortem blood concentrations for persons on therapy with digoxin vary considerably depending on the analytical method used and the anatomical origin of the blood specimen. Concentrations averaged 1.3 μg/L (range, 0.5–2.1) in 18 specimens of serum obtained from the right heart, but these values may be falsely low due to the effect of hemolysis on the ^{3}H-radioimmunoassay used (DiMaio et al., 1975). At the other end of the postmortem "therapeutic" range, Karjalainen et al. (1974) found an average of 4.6 μg/L (range, 1.3–8.2) in 13 samples of blood obtained from an unidentified source using an extraction-radioimmunoassay procedure. Probably the best defined study is that of Holt and Benstead (1975), who determined that complete hemolysis of a blood sample causes a decline of only 12% in the digoxin value relative to plasma; that serum taken from the right heart of 10 patients contained an average of 2.3 μg/L (range, 1.3–3.9) digoxin compared to an average of 1.4 μg/L (range, 0.7–2.9) in serum from the femoral vein of the same subjects; and that equivalent results were obtained for samples analyzed directly with either the ^{3}H or ^{125}I-radioimmunoassay, if correction for color quench was made when using the tritium label. It has been determined that serum digoxin levels nearly always increase after death due to leaching from muscle, with an average postmortem/antemortem ratio ranging from 1.42 for femoral vein blood specimens to 1.96 for heart blood specimens (Vorpahl and Coe, 1978). Fletcher et al. (1979) suggested that postmortem blood samples for digoxin assay be taken from the peripheral circulation within a

few hours after death, that they be completely hemolyzed by freezing and thawing several times, and centrifuged before analysis; the analytical value may then be multiplied by 1.3 to estimate the serum digoxin concentration at the moment of death.

At least 30 digoxin fatalities have been reported in which postmortem blood or serum concentrations were determined; the values range from 3.5–200 μg/L (average, 25) and represent both accidental and intentional overdoses (Iisalo and Nuutila, 1973; Moffat, 1974; Phillips, 1974a; DiMaio et al., 1975; Holt and Benstead, 1975; Ma, 1976; Dickson and Blazey, 1977; Selesky et al., 1977). In 2 digoxin fatalities, concentrations of 200 and 283 μg/L were measured in the left ventricular myocardium (Iisalo and Nuutila, 1973); these concentrations exceed the average therapeutic level for this tissue but are still within the normal range according to the above table. Vorpahl and Coe (1978), in a series of 27 cases, found that vitreous humor digoxin concentrations average 60% those of antemortem serum and 37% those of postmortem heart blood and that they do not change significantly in the first 24 hours after death. Aderjan et al. (1979) recommended that kidney concentrations be measured in the investigation of fatal digoxin poisoning, since this tissue appears to be dramatically elevated in such cases over normal values (140 ± 35 μg/kg). These authors found the following concentrations in a case of suicide by digoxin:

Digoxin Concentrations in a Fatal Case (μg/L or μg/kg)

Blood	Brain	Heart	Lung	Liver	Kidney
22	9.7	43	53	81	1400

Analysis. Digoxin has been successfully quantitated in body fluids by an ATP-ase inhibition technique (Burnett and Conklin, 1971) and by ^{86}Rb uptake inhibition assay (Gjerdrum, 1970). The latter method has been combined with solvent extraction in order to accommodate solid tissues (Andersson et al., 1975). The most frequently used technique for the determination of digoxin is radioimmunoassay (Smith et al., 1969). Certain of the commercially available radioimmunoassay systems are prone to errors from hemolysis, bilirubinemia or abnormal albumin levels (Cerceo and Elloso, 1972); removal of the digoxin from the specimen by extraction or dialysis improves the accuracy of the ^{3}H-radioimmunoassay (Phillips, 1974b), although the development of ^{125}I-systems has circumvented most of the problems associated with earlier assays. The commercial digoxin radioimmunoassay kits exhibit from 0.6–25% cross-reactivity with digitoxin, and many of the digoxin metabolites react to the same degree as digoxin itself (Stoll et al., 1972); on average, only 64% (range, 35–80) of serum digoxin as measured by radioimmunoassay is actually parent drug (Gault et al., 1984). Digoxin-like immunoreactivity has been reported present in the body fluids of individuals not receiving the drug (Balzan et al., 1984; Spiehler et al., 1985); this may be avoided by increasing incubation time during radioimmunoassay or by ultrafiltration of the specimen (Graves et al., 1986; Dasgupta et al., 1990). Thin-layer chromatography (Aderjan et al., 1979), liquid chromatography (Fletcher et al., 1980; Loo et al., 1981; Stone and Soldin, 1988) and solvent extraction (Picotte et al., 1991) have been used prior to immunoassay to provide additional specificity. Liquid chromatography with fluorescence (Kwong and McErlane, 1986; Shepard et al., 1986) or mass spectrometric detection (Tracqui et al., 1997; Guan et al., 1999) has also been reported. Digoxin is stable in blood specimens stored for up to 28 days at room temperature (Revuelta et al., 1996).

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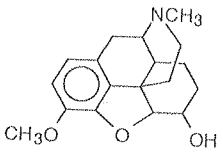
Dihydrocodeine

T½: 3.4–4.5 hr
Vd: 1.0–1.3 L/kg
Fb: ?
pKa: 8.8



Occurrence and Usage. Dihydrocodeine (6-α-hydrocodol, drocode, DHCplus, Synalgos-DC) is a semi-synthetic narcotic analgesic, prepared by the hydrogenation of codeine. It is supplied as the bitartrate salt in 16 mg tablets or capsules for oral administration. Single doses of 16–32 mg may be taken every 4 hours, with a maximum recommended daily limit of 192 mg.

Blood Concentrations. Following a single oral dose of 30 or 60 mg in 7 adult volunteers, peak plasma dihydrocodeine concentrations averaged 0.07 and 0.15 mg/L, respectively, at 1.6 and 1.8 hours post-dose (Rowell et al., 1983). A 60 mg oral dose given to 14 adults resulted in average peak plasma levels of 0.205 mg/L at 1.3 hours for dihydrocodeine and 0.002 mg/L at 1.2 hours for dihydromorphine (Fromm et al., 1995). Twelve healthy men given oral doses of 90 or 120 mg of the drug in a dose-scaling study achieved peak serum dihydrocodeine concentrations averaging 0.22 or 0.27 mg/L, respectively, at 3 hours; peak serum dihydromorphine levels were achieved at 3–5 hours and averaged 2% of the parent drug (Ammon et